federal register

Friday
December 30, 1988

Part VII

Department of Health and Human Services

National Institutes of Health

Recombinant DNA Advisory Committee Meeting; Notice

Recombinant DNA Research; Proposed Actions Under Guidelines; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Advisory Committee; Meeting

Pursuant to Pub. L. 92–463, notice is hereby given of a meeting of the Recombinant DNA Advisory Committee at the National Institutes of Health (NIH), Building 31C, Conference Room 6, 9000 Rockville Pike, Bethesda, Maryland 20892, on January 30, 1989, from approximately 9 a.m. to adjournment at approximately 5 p.m. This meeting will be open to the public to discuss:

Proposed amendment to the Recombinant DNA Advisory Committee Charter;

Proposed revision of NIH Guidelines to refer specifically to research with plants and animals;

Request for permission to perform certain experiments;

Public information brochure on human gene therapy;

Amendment of NIH Guidelines; and

Other matters to be considered by the committee.

Attendance by the public will be limited to space available. Members of the public wishing to speak at the meeting may be given such opportunity at the discretion of the Chair.

Ms. Rachel E. Levinson, Office of Recombinant DNA Activities, National Institutes of Health, Building 31, Room B1C34, Bethesda, Maryland 20892, telephone (301) 496–9838, will provide materials to be discussed at the meeting, rosters of committee members, and substantive program information. A summary of the meeting will be available at a later date.

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592) requires a statement concerning the official government programs contained in the *Catalog of Federal Domestic Assistance*. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined to be not cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the *Catalog of Federal Domestic Assistance* are affected.

Dated: December 27, 1988.

Betty J. Beveridge,

Committee Management Officer, NIH.

[FR Doc. 88–30075 Filed 12–29–88; 8:45 am]

BILLING CODE 4140-01-M

Recombinant DNA Research; Proposed Actions Under Guidelines

AGENCY: National Institutes of Health, PHS, DHHS.

ACTION: Notice of proposed action under NIH Guidelines for Research Involving Recombinant DNA Molecules.

SUMMARY: This notice sets forth proposed actions to be taken under the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules. Interested parties are invited to submit comments concerning these proposals. These proposals will be considered by the Recombinant DNA Advisory Committee (RAC) at its meeting on January 30, 1989. After consideration of these proposals and comments by the RAC, the Director of the National Institutes of Health will issue decisions on these proposals in accordance and with the Guidelines.

DATES: Comments received by January 20, 1989, will be reproduced and distributed to the RAC for consideration at its January 30, 1989, meeting.

ADDRESS: Written comments and recommendations should be submitted to Rachel E. Levinson, Office of Recombinant DNA Activities, Building 31, Room B1C34, National Institutes of Health, Bethesda, Maryland 20892. All comments received in timely response to this notice will be considered and will be available for public inspection in the above office on weekdays between the hours of 8:30 a.m. and 5:00 p.m.

FOR FURTHER INFORMATION CONTACT: Background documentation and additional information can be obtained from the Office of Recombinant DNA Activities, Building 31, Room B1C34, National Institutes of Health, Bethesda, Maryland 20892, (301) 496–9838.

SUPPLEMENTARY INFORMATION: The NIH will consider the following actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules:

I. Proposal To Recommend Amending the Recombinant DNA Advisory Committee Charter

The Recombinant DNA Advisory Committee (RAC) is governed by the provisions of Pub. L. 92–463, the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), which sets forth standards for the formation and use of advisory committees. The RAC operates under terms described in a charter that is approved by the Secretary, Department of Health and Human Services. The Director, National Institutes of Health, has asked the Recombinant DNA Advisory Committee (RAC) to discuss and comment on a proposed amendment to the RAC charter prior to asking the Secretary to consider such an amendment.

The pertinent section of the Charter is as follows:

> There shall be four standing subscommittees and *ad hoc* subcommittees as needed * * * Subcommittees shall be composed of committee members and, as required, of *ad hoc* consultants with expertise in the particular areas addressed by each subcommittee. All subcommittees shall report to the parent committee.

The proposed amendment would be inserted after the paragraph above, as follows:

> All proposals referred to a subcommittee for formal review must be approved by a majority of subcommittee members before being submitted to the parent committee. If a proposal is rejected by a subcommittee, the investigator may appeal this decision by application to the Director, NIH.

II. Proposed Changes in Appendices P and Q of the NIH Guidelines

On August 11, 1987, a "Proposal to Modify and Amend the 'Guidelines for Research Involving Recombinant DNA Molecules' to Refer Specifically to Research with Plants and Animals," was published in the **Federal Register** (52 FR 29800). These amendments would provide containment levels for plants in Appendix P and for animals in Appendix Q. On September 21, 1987, the Recombinant DNA Advisory Committee approved the amendments with certain changes. These changes are summarized here. Paragraph numbers refer to the August 11, 1987, **Federal Register** announcement (52 FR 29800).

4. The second sentence is revised to read as follows:

"Biosafety Level 1 for plants (BL1–P) is designed to provide a moderate level of containment for specific recombinant DNA research involving plants and is

recommended for experiments for which there is convincing biological evidence that precludes the possibility of survival, transfer, or dissemination of the recombinant DNA molecules into the environment, or for which there is no recognizable and predictable risk to the environment in the event of accidental release."

5. The following words in the second sentence are deleted:

"sexual and vegetative reproduction and minimizes."

37. The second sentence is revised to read as follows:

"Animals containing sequences from viral vectors, if the sequences do not lead to transmissible infection either directly or indirectly as a result of complementation or recombination in animals, may be propagated under conditions of physical containment comparable to BL1 or BL1–N and appropriate to the organism under study."

46. Revise by adding "or BL2–P + BC" after "BL3–P."

48a. This paragraph is revised to read as follows:

"III–B–5–d. BL3–P containment is recommended for experiments involving sequences encoding potent vertebrate toxins introduced into plants or associated organisms. Recombinant DNAs containing genes for the biosynthesis of toxic molecules lethal for vertebrates at an LD_{50} of less than 100 nanograms per kilogram body weight fall under Section III–A–1 and require RAC review and NIH and IBC approval before initiation."

50. The second sentence of this paragraph is amended to read as follows:

"Determination of whether or not a pathogen has a potenial for serious detrimental impact on managed (agricultural, forest, grassland) or natural ecosystems should be made by the PI and IBC, in consultation with scientists knowledgeable of plant diseases, crops and ecosystems in the geographic area of the research."

70. The third sentence of this paragraph is amended as follows:

"For certain work with plants, Appendix P replaces Appendix G; it defines Biosaftey Level 1–Plants to Biosafety Level 4–Plants (BL1–P to BL4–P)."

75. Substitute the word "arthropods" for "insects."

87. This sentence is amended to correct a typographical error, as follows:

"Personnel are required to read instructions on BL1–P greenhouse practices and procedures and to follow them."

88. The second sentence of this paragraph is deleted.

89. This sentence is revised to read as follows:

"A record is kept of experiments in progress in the facility."

91a. Substitute the word "arthropod" for "insect."

91b. Substitute the word "arthropods" for both occurrences of the word "insects."

91c. This sentence is deleted.

93a. Delete the word "permanent" in the first sentence.

93c. Substitute the word "arthropods" for "insects."

98. The third sentence of this paragraph is revised to read as follows:

"It should advise personnel of potential consequences if practices are not followed and outline contingency plans in the event containment loss results in release of organisms."

100. The second sentence is amended to read:

"Decontamination of run-off water is not necessarily required."

101. Substitute the word "arthropods" for both occurrences of the word "insects." Change "microorganisms" to "macroorganisms" to correct a typographical error.

103a. This paragraph is deleted.

105. Delete the word "permanent" in the first sentence.

106a. A new sentence is added at the end of this paragraph to read as follows:

"Soil beds are also acceptable unless propagules of experimental organisms are readily disseminated through soil."

106b. The following words are deleted from this paragraph:

"No. 30 mesh (or finer)." The word "insects" is replaced with "arthropods."

108. This sentence is revised to read as follows:

"An autoclave for treatment of contaminated greenhouse materials is available."

114. This first sentence of this paragraph is revised to read as follows:

"All experimental materials, except those that are to remain in a viable or intact state for experimental purposes, are sterilized in an autoclave or rendered biologically inactive before disposal."

115. The word "insect" is replaced with "arthropod."

116. The word "insect" is replaced with "Artropods."

122. The word "permanent" is deleted from the first sentence.

125. The word "permanent" is deleted from the first sentence.

147. The word "Insects" is replaced with "Arthropods."

153. The word "insect" is replaced with "arthropod."

160. The following sentence is deleted from this paragraph:

"A backup source of electricity is provided to run the air handling equipment if the main power source should fail."

171. This sentence is revised to read as follows:

"Ensuring that no organism that can serve as a host promote the transmission of the virus or microorganism is present within a farthest distance that the airborne virus or microorganism may be expected to be effectively disseminated."

173. Replace the word "insect" with "arthropod."

176. Replace the word "insects" with "arthropods."

177. Replace the word "insects" with "arthropods" in both occurrences.

184. The first sentence of this paragraph is amended to read as follows:

"This appendix of the NIH Guidelines specifies containment and confinement practices for research involving whole animals, both those in which the animal's genome has been altered by rcombinant DNA techniques and experiments involving recombinant-DNA-modified nicroorganisms tested on whole animals."

241. This paragraph is amended to read as follows:

"Appendix Q–II–C–1–f. Animals holding areas shall be cleaned at least once a day and decontaminated immediately following any spill of viable materials."

283. This paragraph is amended to read as follows:

"Appendix Q–II–D–1–f. Animal holding areas shall be cleaned at least once a day and decontaminated immediately following any spill of viable materials."

285. Change "18" to "16" in this paragraph.

301. The fourth sentence of this paragraph is amended to read as follows:

"The air pressure within the suit area is to be less than that of any adjacent area."

308. This paragraph is amended to read as follows:

"Appendix Q–II–D–2–u. Respirators shall be worn in rooms containing experimental animals."

328. The third sentence of this paragraph is amended to read as follows:

"It is universally accepted if bacterial spores are used to challenge and verify that the equipment is capable of killing spores then assurance is provided that all other known agents will also be

inactivated by the parameters established to operate the equipment."

After review for consistency with U.S. Department of Agriculture practices, the Agricultural Research Service has recommended the following additional changes. Again, paragraph numbers refer to the original Federal Register announcement.

39. Add: "The containment decision should be consistent with the APHIS Regulations identifying plant pests. 7 CFR Parts 330 and 340, "Plant Pests, Introduction of Genetically Engineered Organisms or Products, Final Rule."

70. Change to read Biosafety Level 4 Plants (BL1–P to BL4–P)."

100. Replace sentence reading "Decontamination of run-off water is not required." with "Run-off water which may contain organisms from the work tray must be appropriately decontaminated."

106b. Insert after "pollen"—"normally 10–20 um in size"

133a. Insert sentence, "A HEPA filter may be used instead of the 80–85% filters and dampers."

227. Insert after "director"—"and IBCs at the sending and receiving institution."

233. Add additional sections: "Appendix Q–II–3–B–f. Floor drains must be permanently capped or screened."

"Appendix Q–II–3–B–g. All perimeter joints and openings must be sealed to form an insect-proof structure.

"Appendix Q–II–3–B–h. All access control door(s) to interior work zone(s) must be appropriately screened (52 mesh)."

"Appendix Q–II–3–B–i. If a forced air ventilation system is provided, vents must be appropriately screened (52 mesh)."

251. Add after "laundered."—"Personnel will shower before exiting the BL3–N area and donning of personal street clothing."

255. Insert after "laboratory director"—"and IBC chairman."

261. Replace "Molded surgical masks or respirators * * *" with "Appropriate respirator protection * * *".

268. Add—"Liquid wastes from shower rooms and toilets may be decontaminated with chemical disinfectants by methods shown to be effective."

270. Add—"if arthropods are used in the experiment or the agent under study can be transmitted by an arthropod, the doors will be appropriately screened."

271. Delete the last half of paragraph, beginning with "The exhaust air from * * *."

275. Add new paragraphs—"Appendix Q–II–C–3–n. Exhaust air from BL3–N containment zone must be appropriately treated by filtering through a single HEPA filter or incinerated before release to the atmosphere. Double HEPA filtration is required if a recombinant DNA-containing organism is excreted in animals and is capable of contaminating the room air at a level to exceed $1x10^4$ organisms per cubic foot of exhausted air. A single HEPA filter must be installed in the inlet air ventilation system. Double HEPA filters are required in the supply air system when a need is identified to equip the exhaust system with double HEPA filters. Heating Ventilation Air Conditioning (HVAC) supply and exhaust ducts and filter housing must have minimal air loss in 20 minutes at 4" of water gauge pressure, or pass a halogen test with a leak rate less than 0.00001 cc/sec at 4" water gauge pressure.

"Appendix Q–II–C–3–o. The integrity of the animal room must have an air leak rate (decay rate) not to exceed 7% per minute (logarithm of pressure against time) over a 20-minute period at 2" of water gauge pressure (rate of decrease is 0.05" wgp/min.)."

308. Replace "Molded surgical masks or respirators" with "Appropriate respirator protection * * *."

325. Delete sentence "Heating Ventilation * * *."

III. Proposal To Clone the Gene Coding for Vancomycin Resistance into Streptococcus Sanguis

Sandra Handwerger, M.D., Beth Israel Medical Center, New York, has requested permission to clone the gene coding for vancomycin resistance from leuconostoc species into streptococcus sanguis via a helper plasmid system. These experiments are covered under Section III–A–2 of the NIH Guidelines which reads: "Deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire it naturally, if such acquisition could compromise the use of the drug to control disease agents in humans or veterinary medicine or agriculture."

IV. Proposal To Amend Appendix H of the NIH Guidelines

The Federal Register of June 24, 1988 (53 FR 23775), contained a proposal by the Postal Service to ban the shipment of all etiologic agents, or materials believed to contain etiologic agents, as defined by the Department of Transportation and the Department of Health and Human Services regulations. Under Appendix H of the current NIH Guidelines for Research Involving Recombinant DNA Molecules of May 7, 1986 (52 FR 16976), this ban could apply to all shipments of recombinant molecules contained within an organism or virus, regardless of whether they are potentially hazardous to human health. Such a ban could inhibit the exchange of scientific information. It could also affect the terms and conditions under which commercial shippers would transport recombinant DNA products. The RAC recognized the potential significance of this issue and referred it to the Definitions Subcommittee of the RAC, which met on December 5, 1988.

A. Proposed Replacement of Appendix H

On December 5, 1988, the Definitions Subcommittee of the RAC unanimously recommended the following replacement of Appendix H of the NIH Guidelines for Research Involving Recombinant DNA Molecules.

"Preamble:

"Recombinant DNA molecules contained in an organism or in a viral genome shall be shipped under the appropriate requirements of the U.S. Public Health Service (42 CFR, Part 72), U.S. Department of Agriculture (9 CFR, subchapters D&E; 7 CFR, Part 340) and/or the U.S. Department of Transportation (49 CFR, Part 173). For purposes of these Guidelines the following recombinant DNA molecules contained in an organism or in a viral genome shall be shipped as etiologic agents: (1) Those listed as class 2, 3, or 4 agents in Appendix B; and/or (2) those contained in reference G–III–2 [1]; and/or (3) those regulated as animal or plant pathogens or pests under titles 7 and 9 CFR; or (4) host organisms containing recombinant DNA derived from those organisms or viral genomes.

"Appendix H–I:

"An illustration of one method of packaging and labeling of recombinant DNA-containing microorganisms and viral genomes defined as etiologic agents in the Premable is shown in Figures 1, 2, and 3. Additional information on packaging and shipping is given in the "Laboratory Safety Monograph-A Supplement to the NIH Guidelines for Recombinant DNA Research," available from the Office of Recombinant DNA Activities and in the Biosafety in Microbiological and Biomedical Laboratories.[1]

"Appendix H–II—Footnote and References of Appendix H 1. Biosafety in Microbial and Biomedical Laboratories, 2nd Edition, (May 1988), U.S. Department of Health and Human Services, Centers for Disease Control, Atlanta, Georgia 30333, and National Institutes of Health, Bethesda, Maryland 20892."

B. Proposed Replacement of the Illustration in Appendix H

The heading changes and the replacement paragraph were written by NIH staff on December 12, 1988, to reflect the intent of the Definitions Subcommittee of the RAC.

The replacement paragraph will read:

"Figures 1, 2, and 3 depict one method for the packaging and labeling of those recombinant DNA-containing organisms and viral genomes defined as etiologic agents in the Preamble of Appendix H. The key features are identified in Figure 1. It is the responsibility of the shipper to comply with the applicable requirements of 42 CFR Part 72 and 49 CFR Part 173 when shipping biological materials or etiologic agents. It is recommended that all organisms containing recombinant molecules, which are exempt and/or class 1 agents, should be shipped in secure, leak-proof containers."

See illustration attached.

BILLING CODE 4140-01-M

FIGURE 1

One Method for

PACKAGING AND LABELING OF ETIOLOGIC AGENTS

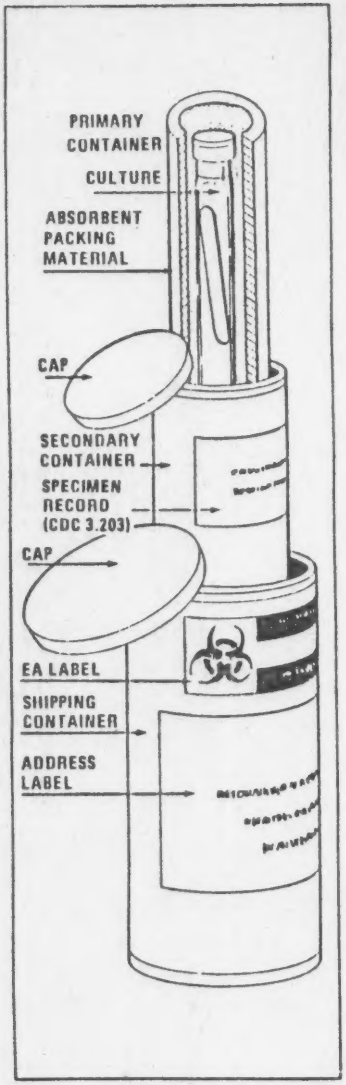
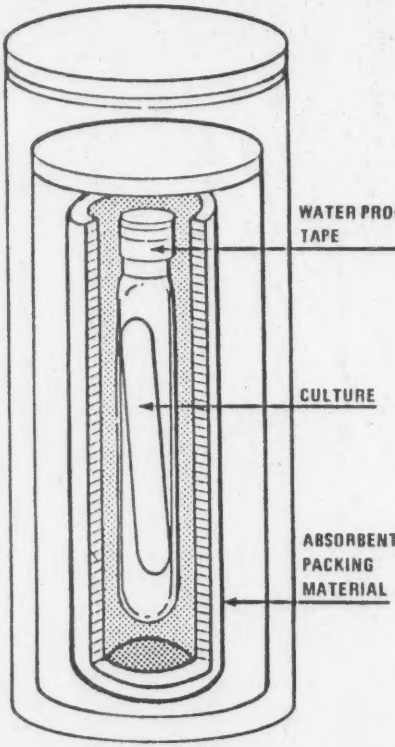


FIGURE 2



CROSS SECTION
OF PROPER PACKING

BILLING CODE 4140-01-C

Replacement paragraph is on attached sheet.

The Interstate Shipment of Etiologic Agents (42 CFR, Part 72) was revised July 21, 1980 to provide for packaging and labeling requirements for etiologic agents and certain other materials shipped in interstate traffic.

Figures 1 and 2 diagram the packaging and labeling of etiologic agents in volumes of less than 50 ml. in accordance with the provisions of subparagraph 72.3 (a) of the cited regulation. Figure illustrates the color and size of the label, described in subparagraph 72.3 (d) (1 - 5) of the regulations, which shall be affixed to all shipments of etiologic agents.

For further information on any provision of this regulation shipping of etiologic agents contact:

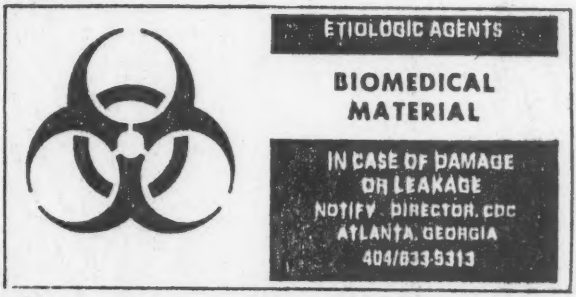
Centers for Disease Control
Attn: Biohazards Control Office
1600 Clifton Road
Atlanta, Georgia 30333

Telephone: 404-639-3883
FTS-236-3883

or Department of Transportation
ATTN: Off. of Hazardous Materials Transp.
400 7th Street, SW
Washington, D.C. 20590
(202) 366-4493

or Department of Agriculture
ATTN: Animal & Plant Hlth. Insp. Serv.
6505 Belcrest Road
Hyattsville, MD 20782
(301) 436-7908

FIGURE 3



V. Review of Public Information Brochure—"Gene Therapy for Human Patients"

The Human Gene Therapy Subcommittee of the Recombinant DNA Advisory Committee has developed a document to be used in educating the nonscientific public about human gene therapy. The information brochure includes background material about the purposes and potential of research in gene therapy, about its supervision, and about why and how the public is involved. The RAC will review the document.

VI. Proposal To Amend Section IV–C—Responsibilities of NIH

The Foundation on Economic Trends and Jeremy Rifkin have submitted a petition to the NIH Office of Recombinant DNA Activities to amend the NIH Guidelines to establish a Human Eugenics Advisory Committee. The proposed amendment is as follows:

Proposed Amendment to the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules To Establish a Human Eugenics Advisory Committee by the Foundation on Economic Trends

November 4, 1988.

Amend Section IV–C–2 as follows: At the end of Section IV–C–2, add the following:

IV–C–2-a. *Human Eugenics Advisory Committee.* The Human Eugenics Advisory Committee (HEAC) is responsible for carrying out specified functions described below as well as others assigned under its charter or by the Secretary, HHS, the Assistant Secretary for Health, and the Director, NIH.

The committee shall consist of eighteen members, including the chair, appointed by the Secretary or his or her designee, as follows:

(1) Three members who are experienced and knowledgeable in protecting the health, safety, and welfare of workers.

(2) Three members who are experienced and knowledgeable in the protection of privacy and civil liberties.

(3) Three members who are experienced and knowledgeable in protecting the rights of the handicapped.

(4) Three members who are experienced and knowledgeable in the abuses and ethical problems in the field of ante-natal and neo-natal testing.

(5) Three members who are experienced in the protection of the interests of consumers, especially in the medical and insurance fields.

(6) Three members who are experienced and knowledgeable in molecular biology and one or more of the following fields: Discrimination in education, bio-ethics, and public affairs.

Groups which have been the traditional victims of past discrimination, including minorities, women, and the disabled shall be well represented on the committee.

All meetings of the HEAC shall be announced in the Federal Register, including tentative agenda items, 30 days in advance of the meeting with final agendas (if modified) available at least 72 hours before the meeting.

The HEAC shall be responsible for advising the Director, NIH, on each and every proposal that involves any human gene therapy, including both somatic cell and germ line therapy. The term "major actions" in Section IV–C–1–b of these Guidelines includes all such proposals. The HEAC chairperson shall be notified of all final decisions by the Director, NIH, on all such proposals in the same manner as the RAC and IBC chairpersons are notified of certain final decisions under Section IV–C–1–b–(1).

Amend Section IV–C–1 to read as follows: Amend the second sentence to read as follows:

The Director has responsibilities under the Guidelines that involve ORDA, the RAC and the HEAC.

After the third sentence of section IV–C–1, add:

Advice from the HEAC is primarily on the ethical, philosophical, social, economic, and eugenic implications and impacts of human genetic therapy.

Amend Section IV–C–1–b by striking all of the language after "Guidelines" and inserting language thereafter so that the text of the provision reads as follows:

In carrying out the responsibilities set forth in this section, the director or a designee shall weigh each proposed action through appropriate analysis and consultation to determine that it complies with the Guidelines, presents no significant risk to health or the environment, and presents no significant risk of (i) adverse impacts on the civil liberties or on the social or economic status of those persons who may be the subject of proposed actions involving gene therapy, (ii) creating undue ethical or philosophical dilemmas or problems for such persons, and (iii) encouraging unsound, undesirable or frivolous human eugenics practices by either public or private institutions or individual practitioners. The term "significant risk" herein includes adverse implications for the interest to be protected.

Amend Section IV–C–1–b–(1) by adding "and the HEAC" after "the RAC" wherever it appears in that provision.

Amend Section IV–C–3–b–(1) by adding "and HEAC" after "RAC" where it appears in the text. In the note that follows the text, add "or a HEAC" before "meeting".

Amend Section IV–C–3–b–(2) by adding "and HEAC" after "RAC" and change "meeting" to "meetings".

Amend Sections IV–C–3–b–(3) and IV–C–3–d by adding "the HEAC" after "RAC".

The reasons for these proposed revisions are set forth in the Petition to the Director accompanying these proposals.

References

Anderson W.F.: 1984, "Prospects for human gene therapy", *Science* 226, 401–409.

Anderson W.F.: 1985, "Human gene therapy: Scientific and ethical considerations", *Journal of Medicine and Philosophy* 10, 275–291.

Anderson W.F. and Fletcher J.C.: 1980, "Gene therapy in human beings: When is it ethical to begin" ?, *New England Journal Medicine* 303, 1293–1297.

Ashley B.M.: 1985, "What does Science say we are" ? *Theologies of the Body: Humanist and Christian*, Chapter 2, The Pope John Center, pp. 19–50.

Bloch N.: 1978, "Reductionism", W.T. Reich (ed.) *Encyclopedia of Bioethics*, Free Press, Macmillan, New York, pp. 1419–1423.

Capron A.M.: 1983, "Don't ban genetic engineering", *Washington Post*, June 16, p. A26.

Davis B.D.: 1983, "The two faces of genetic engineering in man", *Science* 219, 1381.

Department of Health and Human Services: 1986, "National Institutes of Health points to consider in the design and submission of human somaticcell gene therapy protocols", *Recombinant DNA Technical Bulletin* 9(4), 221–242.

Fischhoff B., Lichtenstein S., Slovic P., Derby S.L., Keeney R.L.: 1981, *Acceptable risk*, Cambridge University Press.

Fletcher J.C.: 1983, "Moral problems and ethical issues in prospective human gene therapy", *Virginia Law Review* 69, 515–546.

Fletcher J.C.: 1985, "Ethical issues in and beyond prospective clinical trials of human gene therapy", *Journal of Medicine and Philosophy* 10, 293–309.

Fletcher, Joseph: 1979, "Humanness", in *Humanhood: Essays in Bioethics*, Prometheus Press, New York, pp. 7–19.

Friedmann T. and Roblin R.: 1972, "Gene therapy for human genetic disease" ?, *Science* 175, 949–955.

Glover J.: 1984, *What Sort of People Should There Be?*, Penguin Books, Middlesex, England, pp. 13–56, 178–187.

Gorovitz S.: 1984, "Will we still be 'human' if we have engineered genes and animal organs" ?, *Washington Post*, December 9, pp. C1, C4.

Grobstein C. and Flower M.: 1984, "Gene therapy: proceed with caution", *Hastings Center Report*, 14(2), 13–17.
Kevles D.J.: 1985, *In the Name of Eugenics*, Alfred A. Knopf, New York.
Ludmerer K.M.: 1972, *Genetics and American Society*, The Johns Hopkins University Press, Baltimore.
Manipulating life: ethical issues in genetic engineering, 1982, Church and Society, World Council of Churches, Geneva.
Mercola K.E. and Cline M.J.: 1980, "The potentials of inserting new genetic information", *New England Journal of Medicine* 303, 1297–1300.
Miller H.I.: 1983, "Gene therapy: not to be feared or over-regulated", *Bio/Technology*, June, 382.
Motulsky A.G.: 1983, "Impact of genetic manipulation on society and medicine", *Science* 219, 135–140.
National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: 1978, *The Belmont Report*. Ethical principles and guidelines for the protection of human subjects in research, U.S. Government Printing Office, Washington, DC, DHEW publication no. [OS] 78–0012.
Nelson J.R.: 1984, "From genesis to genetics: a theological-ethical exercise", in *Human Life—A Biblical Perspective for Bioethics*, Fortress Press, Philadelphia, pp. 155–173.
Parliamentary Assemply of the Council of Europe, 33rd Ordinary Session, Recommendation 934 (On genetic engineering), 1982.
Pope John Paul II: 1982, Statement to the Pontifical Academy of Sciences (10/23/82), "Biological research and human dignity", *Origins* 12, 342–343.
Pope John Paul II: 1983, Statement to the World Medical Association (10/29/83), "The ethics of genetic manipulation", *Origins* 13, 385–389.
President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: 1982, *Splicing Life*, U.S. Government Printing Office, Washington, DC.
Rifkin J.: 1983, *Algeny*, Viking Press, New York, pp. 14, 23, 228, 231–234.
Shinn R.L.: 1978, "Gene therapy: ethical issues", in W.T. Reich (ed.) *Encyclopedia of Bioethics*, Free Press, Macmillan, New York, pp. 521–527.
U.S. Congress: 1982, *Human Genetic Engineering*, Hearings Before the Subcommittee on Investigations and Oversight of the Committee on Science and Technology, U.S. Government Printing Office, Washington, DC pp. 2301–2346.
U.S. Congress: 1984, *Human Gene Therapy—A Background Paper*, Office of Technology Assessment, U.S. Government Printing Office, Washington, DC p. 47.
Wade N.: 1982a, "Whether to make perfect humans", *New York Times*, July 22, p. A22.
Wade N.: 1982b, "The rules for reshaping life", *New York Times*, December 29, p. A26.
Walters L.: 1986, "The ethics of human gene therapy", *Nature* 320, 225–227.
Williams D.A. and Orkin S.H.: 1986, "Somatic gene therapy: current status and future prospects", *Journal of Clinical Investigation* 77, 1053–1056.
Williamson R.: 1982, "Gene therapy", *Nature* 298, 416–418.

VII. Proposed Amendment of Section–I–B—Definition of Recombinant DNA Molecules

Section I–B of the NIH Guidelines currently reads as follows:

"I–B—Definition of Recombinant DNA Molecules

"In the context of these Guidelines, recombinant DNA molecules are defined as either (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) DNA molecules that result from the replication of those described in (i) above.

"Synthetic DNA segments likely to yield a potentially harmful polynucleotide or polypeptide (e.g., a toxin or a pharmacologically active agent) shall be considered as equivalent to their natural DNA counterpart. If the synthetic DNA segment is not expressed in vivo as a biologically active polynucleotide or polypeptide product, it is exempt from the Guidelines."

The National Wildlife Federation has submitted a request that the NIH Guidelines "be expanded to encompass research involving organisms engineered by techniques other than recombinant DNA."

The letter proposing this change is as follows:

> The NWF requests that the National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) recommend to the NIH Director that the Guidelines for Research Involving Recombinant DNA Molecules ("Guidelines") be expanded to encompass research involving organisms engineered by techniques other than recombinant DNA.
>
> Expanding the scope of the Guidelines is necessary because recent advances in science have added to the list of techniques capable of producing genetically novel organisms. A growing number of such organisms are *not* subject to the current Guidelines, which provide oversight only of those organisms formed by narrowly defined recombinant DNA techniques. Like recombinant DNA, these new techniques will produce organisms that may pose human health and environmental risks.
>
> We readily acknowledge the difficulty of defining the scope of NIH guidelines in an era of rapid technological change. Although there may be other approaches, to begin the discussion, we propose that Section I–B of the NIH Guidelines, Definition of Recombinant DNA Molecules, be replaced by a new section bringing within the scope of the guidelines all organisms into which foreign DNA has been stably integrated, regardless of technique. We do not propose particular language because we believe that the precise contours of the Guidelines would benefit from thorough discussion by the RAC.

Background

The Guidelines were developed in 1976 to provide standards of safety in research with recombinant DNA techniques. The purpose of the Guidelines was to protect researchers and the public from potential hazards to human health and the environment posed by genetically novel organisms.[1]

The central concern of the NIH was the genetic novelty of the organisms created by recombinant DNA techniques. As the NIH stated in its 1977 Environmental Impact Statement on the Guidelines (2), "[c]oncern over the potential for hazard in organisms containing recombined DNA develops from the central idea that such recombinants will be unique types of organisms, not normally arising in nature, and that their properties will therefore be unknown and unpredictable."

As there was only one technique capable of providing transgenic organisms in 1976, the Guidelines are written to cover only that technique. Current Guidelines (3) apply only to recombinant DNA molecules, which they define "* * * as either (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) DNA molecules that result from the replication of those described in (i) above." This definition captured most genetically novel organisms for review because the recombinant DNA technique depends on joining the foreign DNA to be transferred to vector DNA outside of living cells.

The New Transgenic Techniques

Since that time, scientists have developed other gene transfer techniques (e.g., electroporation, microprojectile techniques, microinjection, chemical poration, cell fusion) that can produce genetically novel organisms but will not necessarily involve "a joining of natural or synthetic segments to DNA molecules" outside living cells. References 4–13 provide a sample of techniques currently capable of producing so-called transgenic organisms—those with DNA from dissimilar parent organisms.

The key to these new transgenic techniques is that they are not dependent upon vectors to transfer the foreign DNA. Although these techniques are not yet well understood, it is known that small pieces of foreign DNA introduced into a cell without vectors can become incorporated into the chromosomes and be expressed.

As a result of these advances, transgenic organisms may be produced by a number of techniques, including, but not limited to recombinant DNA. Transgenic techniques that do not require "recombinant DNA" procedures produce organisms that can be

[1] The 1976 "Decision of the Director, NIH, to Release Guidelines for Research on Recombinant DNA Molecules" (1, p. 27904) declared that "[t]he object of these guidelines is to ensure that experimental DNA recombination will have no ill effects on those engaged in the work, on the general public, or on the environment".

identical to organisms created with recombinant DNA techniques.

RAC members acknowledged the deficiencies in the current Guidelines at June 3, 1988, meeting in a discussion of amendments to the Guidelines regarding transgenic animals (14, 15, 16). Certain experiments with transgenic animals are not subject to the Guidelines because the DNA added to the animals is not "recombinant DNA" as defined by the Guidelines. According to meeting participants,

- "* * * there is a serious and significant loophole that needed to be addressed * * *" (16, p. 18);
- the technology exists to create non-recombinant transgenic organisms ("* * * the technology is moving fast enough that by the time this [transgenic animal amendment] went anyplace that there will be such things", (16, p. 26);
- some transgenic organisms pose hazards ("* * * if you're injecting DNA into an animal * * * you've potentially created something that might be harmful, so you shouldn't let it wild. You couldn't let it out into the wild." (16, p. 39).

Summary

Gene transfer technology has now moved beyond recombinant DNA techniques. The NIH should delay no longer in developing Guidelines that reflect current scientific knowledge so that the public and the environment are protected from potential hazards of the new gene transfer technologies. There is no scientific rationale for limiting oversight to one subset of genetically novel organisms.

We urge the RAC to recommend to the NIH Director that the Guidelines be updated and expanded to encompass all organisms possessing the same degree of genetic novelty as organisms produced by recombinant DNA techniques as currently defined.

We look forward to the RAC's consideration of this request at the January, 1989, meeting. Please call (797–6892) if you have any questions.

Sincerely,

Jane Rissler,

National Biotechnology Policy Center.

References

1. U.S. Department of Health, Education, and Welfare, National Institutes of Health. 1976. Recombinant DNA Research: Guidelines. **Federal Register** 41:27902–27943.

2. U.S. Department of Health, Education, and Welfare, National Institutes of Health. 1977. Environmental impact statement on NIH Guidelines for Research Involving Recombinant DNA Molecules, Part One. DHW Publication No. (NIH) 1489, Bethesda, MD.

3. U.S. Department of Health and Human Services, National Institutes of Health. 1986. Guidelines for Research Involving Recombinant DNA Molecules. **Federal Register** 51:16958–16985.

4. Boynton, J.E., N.W. Gillham, E.H. Harris, J.P. Hosler, A.M. Johnson, A.R. Jones, B.L. Randolph-Anderson, D. Robertson, T.M. Klein, K.B. Shark, and J.C. Sanford. 1988. Chloroplast transformation in *Chlamydomonas* with high velocity microprojectiles. *Science* 240:1534–1538.

5. Hammer, R.E., V.G. Pursel, C.E. Rexroad, R.J. Wall, D.J. Bolt, K.M. Ebert, R.D. Palmiter, and R.L. Brinster. 1985. Production of transgenic rabbits, sheep and pigs by microinjection. *Nature* 315:680–682.

6. Johnston, S.A., P.A. Anziano, K. Shark, J.C. Sanford, and R.A. Butow. 1988. Mitochondrial transformation in yeast by bombardment with microprojectiles. *Science* 240:1538–1541.

7. Klein, T.M., T. Gradziel, M.E. Fromm, and J.C. Sanford. 1988. Factors influencing gene delivery into *Zea mays* cells by high-velocity microprojectiles. *Bio/Technology* 6:559–563.

8. Klein. T.M., E.D. Wolf, R. Wu, and J.C. Sanford. 1987. High-velocity microprojectiles for delivering nucleic acids into living cells. *Nature* 327:70–73.

9. McCabe, D.E., W.F. Swain, B.J. Martinell, and P. Christou. 1988. Stable transformation of soybean *(Glycine max)* by particle acceleration. *Bio/Technology* 6:923–926.

10. Morikawa, H., K. Sugino, Y. Hayashi, J. Takeda, M. Senda, A. Hirai, and Y. Yamada. 1986. Interspecific plant hybridization by electrofusion in *Nicotiana. Bio/Technology* 4:57–60.

11. Nishiguchi, M., W.H.R. Langridge, A.A. Szalay, and M. Zaitlin. 1986. Electroporation-mediated infection of tobacco leaf protoplasts with tobacco mosaic virus RNA and cucumber mosaic virus RNA. *Plant Cell Reports* 5:57–60.

12. Sanford, J.C., T.M. Klein, E.D. Wolf, and N. Allen. 1987. Delivery of substances into cells and tissues using a particle bombardment process. *Particulate Science and Technology* 5:27–37.

13. Toneguzzo, F. and A. Keating. 1986. Stable expression of selectable genes introduced into hematopoietic stem cells by electric field-mediated DNA transfer. *Proceedings National Academy of Science* 83:3496–3499.

14. U.S. Department of Health and Human Services, National Institutes of Health. 1988. Recombinant DNA Research Guidelines and Advisory Committee Meeting; Notices. **Federal Register** 53:12753–4.

15. U.S. Department of Health and Human Services, National Institutes of Health, Working Group on Transgenic Animals, Recombinant DNA Advisory Committee. 1988. Minutes of meeting, March 28, 1988. *Recombinant DNA Technical Bulletin* 11:25–30.

16. U.S. Department of Health and Human Services, National Institutes of Health, Recombinant DNA Advisory Committee. 1988. Transcript of the June 3, 1988, meeting. StenoTech, Inc., Gaithersburg, MD.

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined to be not cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

Dated: December 23, 1988.

William F. Raub,

Acting Director, National Institutes of Health.

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